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Most deaths in Western countries can currently be associated with fibrotic diseases. During fibrosis excessive amounts of extra-cellular matrix components, such as collagen, are deposited in tissues, which can lead to tissue stiffness and organ failure. The underlying mechanisms leading to tissue fibrosis remain poorly understand and, consequently, our capacities to treat fibrotic diseases remain limited. Currently approved drugs only delay the progression of fibrosis and are often associated with severe side-effects, which limit their clinical application. Thus, a better understanding of the ontology of fibrotic diseases and the development of more specific and more efficient drugs for the treatment of tissue fibrosis is an urgent clinical meet.

Myofibroblasts are the major producers of extra-cellular matrix components and an expansion of myofibroblasts is observed during fibrosis. In mice, it is well established that blood vessel associated pericytes are the major source of myofibroblasts in fibrotic tissues [1]. In particular, the local activation of the Transforming Growth Factor beta (TGFβ) induces the differentiation of pericytes into myofibroblasts during the development of tissue fibrosis [1]. The Epidermal Growth Factor (EGF) like growth factor Amphiregulin has recently been identified as being a critical factor that induces this local activation of TGFβ on pericytes and thus their differentiation into myofibroblasts [2]. Amphiregulin is a cytokine, involved in immunity against helminth infection, in immune regulation and in wound repair [3]. In accordance with the finding that Amphiregulin is an important driver for myofibroblast differentiation under inflammatory conditions, it has also been shown in various different model systems that Amphiregulin deficient mice are resistant to the development of tissue fibrosis [4], while the injection of recombinant Amphiregulin into mice can induce fibrosis. However, these different mouse models are rather short-term models, while the ontology of human fibrotic diseases, based on chronic, local inflammation can stretch over several years. Furthermore, in human fibrotic diseases an Epithelial-Mesenchymal-Transition (EMT) seems to contribute to the expansion of myofibroblasts. Also EMT is a TGFβ-driven process; nonetheless, these differences between humans and mouse models raised the question whether the underlying mechanisms for the development of tissue fibrosis can be translated into a human setting. In particular, whether Amphiregulin is also a driver of tissue fibrosis in humans.

In this regard, a recent publication by Todd et al. constitutes a major step forward [5]. The authors studied chronic lung allograft dysfunction (CLAD), a chronic inflammatory disease in lung transplant patients, which is characterized by excessive matrix deposition, leading to loss of lung function. They followed two cohorts of lung-transplant patients, who either developed CLAD or not. They found that the expression of Amphiregulin in the lungs of patients with CLAD is significantly higher than in those without CLAD. Critically, the authors also followed individual patients in a longitudinal study and found that increases in Amphiregulin expression in the lungs of patients directly correlated with the development of CLAD. Given the findings in mouse models, these data derived from these patient cohorts strongly suggests that also in CLAD patients Amphiregulin is a major driver of tissue fibrosis.

The finding that an EGF-like growth factor could contribute to tissue fibrosis may appear counter-intuitive at first, as a substantial fraction of cancer patients being treated with EGFR inhibitors develop lung fibrosis. But not only the low-affinity EGFR ligand Amphiregulin plays a critical role in the development of tissue fibrosis, but also the high-affinity ligand heparin-binding EGF-like growth factor (HB-EGF). The EGFR shows a so-called “agonistic bias”,

which means that ligands with different affinities induce the activation of different down-stream signalling pathways (Figure 1). Consequently, the low affinity-ligand Amphiregulin induces the activation of TGFβ (Minutti), while the high-affinity ligand HB-EGF activates the intracellular inhibitor of TGFβ-signalling TIGIF; in this way, preventing the differentiation of pericytes into myofibroblasts [6]. As a consequence, *Hbegf*$^{-/-}$ mice develop more severe forms of tissue fibrosis [6]. The application of EGFR inhibitors in patients may thus block this HB-EGF-mediated physiological counterbalance to TGFβ signalling and may thereby allow for the progression of an underlying form of tissue fibrosis in EGFR inhibitor treated cancer patients.

Thus, taken together, the publication by Todd et al. [5] suggests a novel more refined approach for the treatment of tissue fibrosis, by targeting specifically Amphiregulin function. Furthermore, treating patients with lung transplants with such drugs could be an attractive first target group, as the development of CLAD is a rather frequent and predictable event, which could precisely be measured during clinical trials. Success of such drugs, such as for instance an Amphiregulin-neutralizing antibody, could then open the opportunity of applying such a drug to other fibrotic diseases and thus creating hope for resolving a major unmet clinical need.

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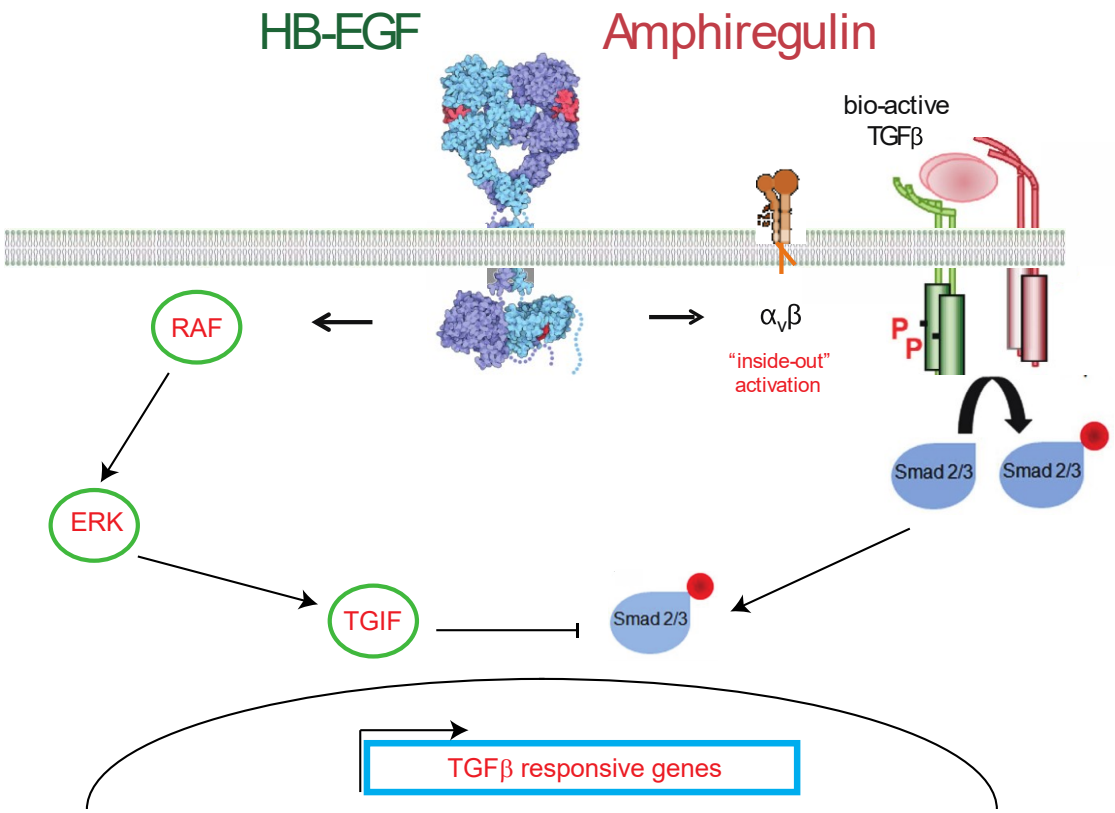

Figure 1: The differential expression of two antagonistic EGF-like growth factors determines the functionality of local TGFβ.
The low affinity EGFR ligand Amphiregulin induces a sustained activation of PLCγ signalling. Such signalling induces the "inside-out" activation of integrin-αv and thus the local, integrin-mediated release of bio-active TGFβ. In contrast, the high-affinity EGFR ligand HB-EGF induces the activation of the MAPK signalling pathway. The pronounced ERK activation induces the accumulation of TGIF, an intracellular repressors of TGFβ signalling. (HB-EGF induced EGFR signalling is depicted in green, while Amphiregulin induced EGFR signalling is depicted in red. TGFβ signalling is depicted in blue.)